substituent, could be expected to accentuate the required differences in axial bond lengths with changes in the ϕ angle. This appears to be observed in the two complexes at hand. [Fe(TPP)(2-MeIm)$_2$]ClO$_4$ has two independent ligand orientations with ϕ for both $\approx$32°. As noted previously, ϕ for [Fe(OEP)(2-MeIm)$_2$]ClO$_4$ is 22°. Nonbonded contacts between imidazole carbon atoms (both the unsubstituted α-carbon atom and the methyl carbon atom) are relatively short (2.92–3.22 Å) in both species. Surprisingly, perhaps, the shortest nonbonded contact is always between the unsubstituted α-carbon atom, not the methyl carbon atom, and porphinato core atoms. Calculation of H atom⋯core contacts for both species leads to similar results.[34] The differences in the nonbonded contacts between the two species are only about half of the 0.26-Å difference in axial bond length as a result of the differing orientation of 2-methylimidazole and core conformations. Additional model calculations for [Fe(OEP)(2-MeIm)$_2$]ClO$_4$ with the observed orientation of the 2-MeIm ligand, but with low-spin Fe–N bond distances (2.012 Å), yield shortened H⋯core contacts of ~2.30 Å. These contacts increase by ~0.10 Å for a 10° rotation of the ligand to ϕ = 32°. We conclude that even a 10° rotation of the axial 2-methylimidazole ligand could be sufficient to require a significant lengthening of the axial bond(s) on the basis of nonbonded packing considerations. These lengthened bonds, in turn, can only be achieved in an intermediate- or high-spin form of the complex.[1] Such bond length–lignad rotation correlations could arise only when the different spin states were energetically similar such as in a spin-equilibrium complex.

The orientation of the axial ligands are, of course, firmly fixed in the solid state. In solution the ligands are freer to rotate around the axial Fe–N bonds.[35] Thus it is reasonable to expect a range of ligand orientations that would allow axial bond elongation and contraction appropriate for the thermal population of the high- and low-spin forms of the molecule. This bond-length variation is not possible in the lattice of [Fe(OEP)(2-MeIm)$_2$]ClO$_4$; the state-dependent magnetic susceptibilities are readily understood as a thermal spin-equilibrium system in solution and a high-spin conformer trapped in the solid state. For [Fe(TPP)(2-MeIm)$_2$]ClO$_4$, the spin equilibrium is shifted more toward the low-spin form in solution and the low-spin state is trapped in the solid. For both species, the solution ground state is low spin.

The foregoing rotational effects are directly applicable to 2-substituted imidazole and unsubstituted pyridine complexes, but not unsubstituted imidazole complexes of unconstrained iron porphyrinates. These effects could be applicable in hemoproteins if the protein could affect both the rotational orientation of the histidine ring and the tilt (nonequal Fe–N–C(α) angles) of the ring. Indeed, such efforts have been suggested as important components of the allosteric mechanism of hemoglobin oxygenation.[36]

Acknowledgment. We thank Professors J. L. Hoard and C. A. Reed for information on [Fe(TPP)(2-MeIm)$_2$]ClO$_4$ in advance of its complete publication. We also thank Prof. C. A. Reed for the SQUID susceptibility measurements, Prof. R. G. Hayes for assistance with EPR measurements, and the National Institutes of Health for support of this work under Grant HL-15627. We thank Prof. K. Hatano for stimulating discussions on bis(imidazole) complexes and Prof. C. E. Strouse for a copy of K. R. Levan's thesis.

Registry No. [Fe(OEP)(2-MeIm)$_2$]ClO$_4$, 92055-42-0; [Fe(OEP)-OClO$_3$], 50540-30-2.

Supplementary Material Available: Table II, anisotropic temperature factors, Table III, fixed hydrogen atom coordinates, and listings of the observed and calculated structure amplitudes (×10) for [Fe(OEP)(2-MeIm)$_2$]ClO$_4$ (28 pages). Ordering information is given on any current masthead page.

---

[34] Calculation of nonbonded distances used the observed methyl group orientation in [Fe(OEP)(2-MeIm)$_2$]ClO$_4$ and an idealized version (C–H vector planar with the imidazole ring) for [Fe(TPP)(2-MeIm)$_2$]ClO$_4$. The C–H distance used was the equilibrium distance of 1.08 Å. The H⋯core atom distances ranged from 2.55 Å upward for the OEP derivative and 2.41 Å upward for the TPP derivative.

(35) A referee has noted the possibility of an electronic effect on the d-orbital splittings by a ϕ-dependent mixing with the 2-MeIm orbitals. We agree that such an effect is possible and may account for the fact that the observed ϕ values tend to be small values in imidazole-ligated metalloporphyrins. We are inclined to believe that the magnitude of the effect is not sufficient to cause a spin-state change (note, for example, that ϕ ranges from near 0° to 32° in the low-spin bis(imidazole)ferric systems).

(36) Baldwin, J.; Chothia, C. *J. Mol. Biol.* **1979**, *129*, 175–220.

Kinetics of Reversible Intramolecular Elimination Reactions. 1. An Apparent E2 Elimination of a β-Acyloxy Ketone

Barbara J. Mayer,[†‡] Thomas A. Spencer,[*†] and Kay D. Onan[§]

Contribution from the Departments of Chemistry, Dartmouth College,
Hanover, New Hampshire 03755, and Northeastern University, Boston, Massachusetts 02115.
Received November 21, 1983

Abstract: The elimination reactions of β-acyloxy ketone **7** and β-acetoxy ketone **1** are both subject to catalysis by hydronium ion, hydroxide ion, and general bases, but the reaction of **7** differs markedly from that of **1**. The reaction of **7** is reversible, and equilibrium amounts of the product enone vary from 16% at pH <3.5 to 100% at pH >7. In addition, **7** reacts from 50 to 10^4 times more rapidly than **1** with basic catalysts ranging in pK_a from 15.7 to 3.3. The Brønsted β for general base catalysis of the E1cB$_1$ reaction of **1** is 0.69, but for the reaction of **7** β = 0.42. That both reactions involve rate-limiting proton removal is evidenced by large invariant primary kinetic isotope effects. These observations lead to the proposal that **7** reacts by an E2 mechanism, previously unobserved in an alkene-forming elimination involving a proton α to a carbonyl group.

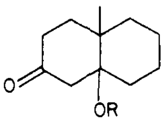
Previous studies in this laboratory have shown that the essentially quantitative and irreversible general base catalyzed elimination reactions of **1**, **2**, **3**, and **4** to form enone **5** in aqueous solution proceed by a stepwise mechanism through formation of intermediate enolate anions, **6**.[1-3] Under all conditions used,

---

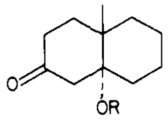
[†] Dartmouth College.
[‡] Present address: Department of Chemistry, California State University, Fresno, Fresno, CA 93740.
[§] Northeastern University.

(1) Hupe, D. J.; Kendall, M. C. R.; Spencer, T. A. *J. Am. Chem. Soc.* **1972**, *94*, 1254–1263.

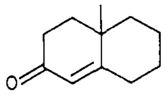
0002-7863/84/1506-6343$01.50/0



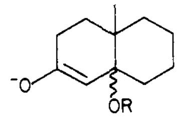
1, R = COCH$_3$
2, R = H



3, R = COCH$_3$
4, R = H



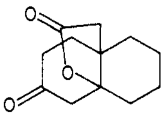
5



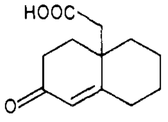
6, R = H or COCH$_3$

proton removal from β-acetoxy ketones **1** and **3** to form **6** is rate limiting (E1cB$_1$).[1,3] With hydroxy ketones **2** and **4**, which contain a much poorer leaving group, hydroxide ion, proton removal is rate limiting under conditions of low hydroxide ion and general base concentration.[2,3] However, if the pH or general base concentration is increased, proton removal from **2** and **4** becomes rapid and reversible, and expulsion of the leaving group from **6** becomes rate limiting (E1cB$_R$ mechanism).[2,3]

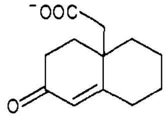
This paper describes a study of the elimination reaction of lactone **7**, the preparation of which we have previously described,[4] to form enone acid **8** or its conjugate base **9**. This reaction, unlike



7



8



9

those of **1–4**, is readily reversible. Its study was undertaken with the hope of elucidating catalysis of the conjugate addition step leading from **8** or **9** to **7**. As it turned out, the kinetic behavior of **7** is unexpectedly and distinctly different from that of **1** and **3**, and, on the basis of the results described herein, we are led to propose a concerted elimination (E2 mechanism) for the conversion of **7** to **9**.

Results and Discussion

Equilibria and Catalysis by Hydronium and Hydroxide Ions. When a solution prepared by dissolving **7** in aqueous base is allowed to equilibrate, one observes UV absorption with λ_{max} = 247.5 nm and ϵ = 14 500 based on the assumption that complete conversion to anion **9** has occurred. If this solution is rapidly acidified, λ_{max} shifts to 244.7 nm with an apparent value of ϵ for enone acid **8** of 15 400. The absorbance of such an acidified solution decreases rapidly upon standing, presumably reflecting reconversion of **8** to **7**. Attempts to isolate **8** were unsuccessful because the material obtained was always at least partially **7**.

The shift in λ_{max} from 247.5 to 244.7 nm upon acidification is a consequence of protonation of the carboxylate anion of **9** rather than the change in the pH of the medium, because the λ_{max} of enone **5** is independent of pH. The probable explanation for the shift to longer wavelength when **8** is ionized is that the carboxylate anion of **9** electrostatically stabilizes the enhanced positive charge which exists at the β carbon of the enone in its excited (π^*) state relative to its ground state. Kosower and Remy[5] report a shift from 232.5 to 229 nm upon quaternization of the nitrogen atom in enone **10**, a change which they explain in terms of destablization of the π^* state by repulsion of the positively charged nitrogen and the enhanced positive charge at the β carbon. It seems reasonable that the opposite effect accounts for the difference in λ_{max} between **8** and **9**.

The equilibrium compositions of solutions of **7** plus **8** and/or **9** were determined from their UV absorption at different pH's. The results, shown in Figure 1, indicate that the amount of enone (**8** and/or **9**) present at equilibrium ranges from 16% at pH $\leq$3 to 100% at pH $\geq$7. The observation of 84% **7** in equilibrium with **8** at low pH contrasts with the essentially quantitative conversion of β-acetoxy ketones **1** and **3** to enone **5** and acetic acid at all pH's. This difference can be readily explained, however, if the reverse reaction of **8** to give **7** is sufficiently facilitated by a large effective molarity (EM) of the carboxylic acid moiety of **8**. Postulation of such a large EM seems very reasonable on the basis of numerous precedents in intramolecular nucleophilic additions.[6]

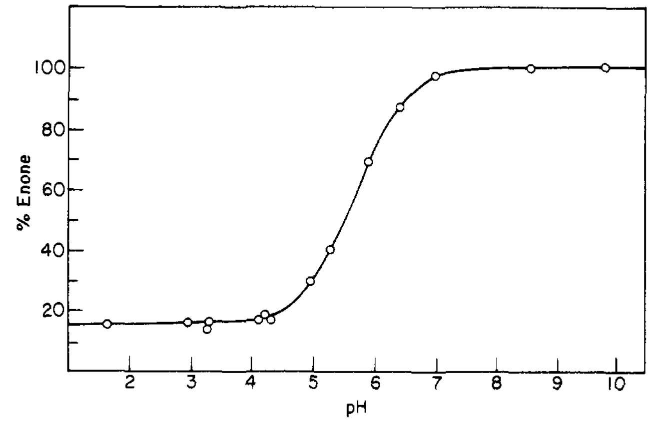


Figure 1. Equilibrium between **7** and **8** or **9**. The open circles are experimentally determined points, and the solid line is calculated from eq 4 as described in the text.

The approach to an equilibrium mixture of **7** and **8** can be studied either by following the increase in the UV absorption of a solution of **7** or by following the decrease in UV absorption of a solution of **8**, which can be prepared by rapid acidification of a solution of **9** to pH $\leq$3. In acidic solutions the approach to equilibrium from either **7** or **8** is a pseudo-first-order process, characterized by a rate constant, k_{obsd}, which is the sum of the rate constants for the forward reaction (k^f) and the reverse reaction (k^r). These reactions are catalyzed by hydronium ion and are described by the rate laws given in eq 1 and 2, where [H$_3$O$^+$] is a_H as measured by pH meter, $k_H{}^f[H_3O^+] = k^f$, and $k_H{}^r[H_3O^+] = k^r$.

$$d[\mathbf{8}]/dt = k_{obsd}\,[\mathbf{7}] = (k_H{}^f + k_H{}^r)[H_3O^+][\mathbf{7}] \tag{1}$$

$$-d[\mathbf{8}]/dt = k_{obsd}\,[\mathbf{8}] = (k_H{}^f + k_H{}^r)[H_3O^+][\mathbf{8}] \tag{2}$$

The relative magnitudes of k^f and k^r can be calculated from the experimental values of K_e and k_{obsd}, using the expression $k^f = k_{obsd}/(1 + 1/K_e)$.[7] The experimentally determined rate constants, $k_H{}^f$ and $k_H{}^r$, are the same whether appearance or disappearance of **8** is monitored.

The value of $k_H{}^f$ is 3.2 × 10^{-4} M^{-1} s^{-1}, and the value of $k_H{}^r$ is 1.66 × 10^{-3} M^{-1} s^{-1}. This value of $k_H{}^f$ is comparable in magnitude to the second-order rate constants for hydronium ion catalysis of similar elimination reactions studied in this[1-3] and other[8] laboratories. The value of k_H for **1** → **5**, for example, is 8.0 × 10^{-5} M^{-1} s^{-1};[1] for **2** → **5**, k_H = 3.0 × 10^{-5} M^{-1} s^{-1};[2] and for 4-phenyl-4-hydroxy-2-butanone, k_H = 1.6 × 10^{-5} M^{-1} s^{-1}.[8] These rate constants are also similar to the observed value,[9] 2.7 × 10^{-5} M^{-1} s^{-1}, for the rate constant for hydronium ion catalyzed enolization of acetone, which has been shown by Bell and Jones[9] to occur via equilibrium protonation of the carbonyl oxygen followed by rate-limiting α-proton abstraction. The differences in these values correspond to the expected increase in α-carbon acidity upon varying the β substituent.[10] It is highly probable

---

(2) Hupe, D. J.; Kendall, M. C. R.; Sinner, G. T.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 2260–2270.

(3) Roberts, R. D.; Ferran, H. E., Jr.; Gula, M. J.; Spencer, T. A. *J. Am. Chem. Soc.* **1980**, *102*, 7054–7058.

(4) Gula, M. J.; Spencer, T. A. *J. Org. Chem.* **1980**, *45*, 805–809.

(5) Kosower, E. M.; Remy, D. C. *Tetrahedron* **1959**, *5*, 281–287.

(6) Kirby, A. J. "Advances in Physical Organic Chemistry"; Gold, V., Bethel, D., Eds.; Academic Press: New York, 1980; Vol. 17, pp 183–278.

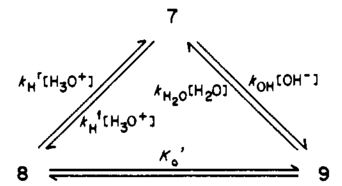
(7) Jencks, W. P. "Catalysis in Chemistry and Enzymology"; McGraw-Hill: New York, 1969.

(8) Noyce, D. S.; Reed, W. L. *J. Am. Chem. Soc.* **1958**, *80*, 5539–5542.

(9) Bell, R. P.; Jones, P. *J. Chem. Soc.* **1953**, 88–92.

(10) More O'Ferrall, R. A.; Warren, P. J. *J. Chem. Soc., Chem. Commun.* **1975**, 483–484. Cavestri, R. C.; Fedor, L. R. *J. Am. Chem. Soc.* **1970**, *92*, 4610–4613.

Scheme I



that all the elimination reactions cited above also proceed via rate-limiting enol formation.

The fact that the measured values of k_H^f and k_H^r are not dependent on the direction from which equilibrium is approached shows that the concentration of intermediate enol is always negligible. This is in accord with recent results[11] which indicate that the rate constant for acid-catalyzed ketonization of cyclohexanone enol is 6 orders of magnitude greater than k_H^f or k_H^r.

In aqueous solutions having pH ≥7, the elimination reaction of $\mathbf{7} \rightarrow \mathbf{9}$ apparently proceeds to completion, as noted earlier. This reaction is catalyzed by hydroxide ion, and pseudo-first-order kinetics are observed if excess hydroxide ion is present. The reaction obeys the rate law given in eq 3, and the value of k_{OH} is 65 $M^{-1}\ s^{-1}$.

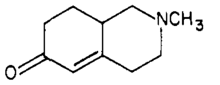
$$d[\mathbf{9}]/dt = k_{OH}[OH^-][\mathbf{7}] \tag{3}$$

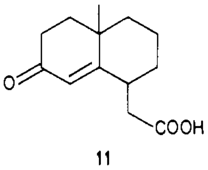
Using the experimentally measured rate constants k_{OH}, k_H^f, and k_H^r, it is possible to derive an equation for the equilibrium constant, K_e, for the equilibrium between **7** and **8** and/or **9** as a function of pH, where $K_e \equiv [\mathbf{8} + \mathbf{9}]/[\mathbf{7}]$. According to this definition, K_e is equal to the sum of the equilibrium constants for the two individual equilibria, $\mathbf{7} \rightleftharpoons \mathbf{8}$ and $\mathbf{7} \rightleftharpoons \mathbf{9}$, shown in Scheme I. These equilibrium constants can be determined from the ratio of the rate constants for the forward reaction to the rate constants for the reverse reaction for each equilibrium. The expression for K_e is given in eq 4.

$$K_e = \frac{k_H^f}{k_H^r} + \frac{k_{OH}K_W}{k_{H_2O}[H_2O]}\frac{1}{[H^+]} \tag{4}$$

The solid line in Figure 1 was calculated by using eq 4. Initially, K_e was determined from a single experimental point, and a value for $k_{H_2O} = 1.6 \times 10^{-9}\ M^{-1}\ s^{-1}$ was calculated from eq 4. This value was then used in eq 4 to calculate the curve in Figure 1.

The third individual equilibrium shown in Scheme I, $\mathbf{8} \rightleftharpoons \mathbf{9}$, can be used to determine the pK_a of **8**, which, as noted earlier, cannot be measured directly because pure **8** cannot be isolated. As written in Scheme I, the equilibrium is $\mathbf{8} + OH^- \rightleftharpoons \mathbf{9} + H_2O$, with equilibrium constant K_a', rather than the customary $H_2O + \mathbf{8} \rightleftharpoons \mathbf{9} + H_3O^+$, which defines K_a for **8**. Since the equilibrium constants for $\mathbf{7} \rightleftharpoons \mathbf{8}$ and $\mathbf{7} \rightleftharpoons \mathbf{9}$ are known, the value of K_a' can easily be calculated and then converted, using $K_a = K_a'K_W/[H_2O]$, to a value of $K_a = 3.8 \times 10^{-5}$ for **8**. This calculated pK_a of 4.4 for **8** is reasonable for a simple carboxylic acid[12] and is not very different from the pK_a of 4.65 determined for keto acid **11**.[13]


10



11

The value of k_{OH} of 65 $M^{-1}\ s^{-1}$ for the reaction $\mathbf{7} \rightarrow \mathbf{9}$ is of particular interest because it is surprisingly large. Whereas there is only a 4-fold difference between the rate constants for hydronium ion catalyzed enolization of **7** vs. **1**, k_{OH} for **7** is 54 times greater than k_{OH} for **1**. This difference in k_{OH} was unexpected since the values of k_{OH} for proton removal from **1–4** differ by less than a factor of 10,[1-3] and in a manner consistent with the difference in inductive effects of the leaving groups on the acidity of the α carbon.[10] Cavestri and Fedor also found a very small increase in the rate of α-proton removal with increasing leaving-group ability for 4-(4-substituted-benzoyloxy)-2-butanones,[10] consistent with the small increase observed for **1** and **3** compared to **2** and **4**.

Table I. Rate Constants for the Reactions of **7** and **1** in Water at 25 °C and μ = 0.4 (KCl)

catalyst	pK_a[a]	k_B, k_{OH}, k_H^f, or k_B^f for **7**,[c] $M^{-1}\ s^{-1}$	k_B, k_{OH}, or k_H for **1**,[c] $M^{-1}\ s^{-1}$	$k(\mathbf{7})/k(\mathbf{1})$
hydroxide ion	15.7	65	1.2[b]	54
quinuclidine	11.2	28	0.4[b]	70
3-hydroxyquinuclidine	9.9	14	6.6×10^{-2} ($\pm 1.0 \times 10^{-2}$)	212
3-chloroquinuclidine	8.7	4.7	1.9×10^{-2}	247
Dabco	8.7	5.3	2.2×10^{-2}[b]	241
3-quinuclidinone	7.2	0.8 (±0.1)	1.2×10^{-3}	666
Dabco·H^+	3.3	1.6×10^{-2}	1.7×10^{-6}	9412
hydronium ion	−1.7	3.2×10^{-4}	8.0×10^{-5}[b]	4

[a] Determined at 25 °C and μ = 0.4 (KCl) as described in the Experimental Section. [b] Determined previously by Hupe et al.[1] [c] The error in the rate constants is typically <5%, and unless noted, is always <10%.

General Base Catalysis. The reaction of **7** to form **9** in aqueous solution at pH >7 is subject to general base catalysis. Kinetic runs with differing concentrations of tertiary amine buffers yielded the rate law given in eq 5.

$$d[\mathbf{9}]/dt = (k_{OH}[OH^-] + k_B[B])[\mathbf{7}] \tag{5}$$

It was immediately and strikingly apparent that the values of k_B, like k_{OH}, were much larger than the corresponding values of k_B previously obtained for the conversion of **1** to **5**,[1] and that the difference increased with decreasing base strength. In order to put this comparison on a quantitative basis, it was decided to determine k_B as a function of catalyst pK_a for both **7** and **1**, using the same set of tertiary amines as general bases for each substrate. Since preliminary observations[14] had indicated that **7** was at least as sensitive to the effects of steric congestion as **1**,[1] a series of structurally similar unhindered bicyclic amines was used to elucidate the Brønsted behavior. These catalysts, listed in Table I, provided a range of pK_a from 11.2 to 3.3 with negligible difference in steric hindrance around the proton-accepting nitrogen atom.

With the weakly basic amine, monoprotonated 1,4-diazabicyclo[2.2.2]octane (Dabco·H^+, pK_a = 3.3), as buffer, the reaction proceeds to an equilibrium mixture of **7** and **8**, as discussed earlier. The rate law given in eq 6 is observed, where $k^f = k_H^f[H_3O^+] + k_B^f[B]$ and $k^r = k_H^r[H_3O^+] + k_B^r[B]$.

$$d[\mathbf{8}]/dt = [(k_H^f + k_H^r)[H_3O^+] + ((k_B^f + k_B^r)[B])[\mathbf{7}] \tag{6}$$

The values of the first-order rate constants for $\mathbf{7} \rightarrow \mathbf{8}$ (k^f) and $\mathbf{8} \rightarrow \mathbf{7}$ (k^r) were determined from K_e and k_{obsd} as described earlier for the hydronium ion catalyzed reaction, and k_B^f and k_B^r were determined from the slopes of plots of k^f and k^r vs. [B], respectively.

The values of k_B obtained for **7** and **1** are given in Table I, and the Brønsted plots for the two substrates are shown in Figure 2. The Brønsted behavior of **7** is obviously different from that of **1**. With the strongest base in the series, quinuclidine (pK_a = 11.2), k_B is 70 times larger for **7** than for **1**.[1] With the weakest base in the series, Dabco·H^+, the difference between k_B^f for **7** and k_B for **1** is a factor of 10^4. For **7**, the Brønsted β is 0.42, which

---

[11] Dubois, J.-E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* **1981**, *103*, 5393–5401.

[12] Bell, R. P. "Acids and Bases"; Methuen and Co. Ltd.: London, 1969; Chapter 5, pp 50–63.

[13] Jacob, J. N.; Nelson, J. A.; Spencer, T. A. *J. Org. Chem.* **1980**, *45*, 1645–1650. The pK_a of **11** was determined by: Jacob, J. N., unpublished work.

[14] Mayer, B. J.; Spencer, T. A.; unpublished results. The k_B^f's determined were as follows: *N*-methylmorpholine (pK_a = 7.4), $2.7 \times 10^{-2}\ M^{-1}\ s^{-1}$; imidazole ($pK_a$ = 6.95), $4.1 \times 10^{-2}\ M^{-1}\ s^{-1}$; acetate ($pK_a$ = 4.75), $7.2 \times 10^{-4}\ M^{-1}\ s^{-1}$, ($k_B^r = 2.2 \times 10^{-3}\ M^{-1}\ s^{-1}$); and *N*,*N*-dimethylcyanomethylamine (pK_a = 4.2), $1.1 \times 10^{-2}\ M^{-1}\ s^{-1}$, ($k_B^r = 2.8 \times 10^{-2}\ M^{-1}\ s^{-1}$).

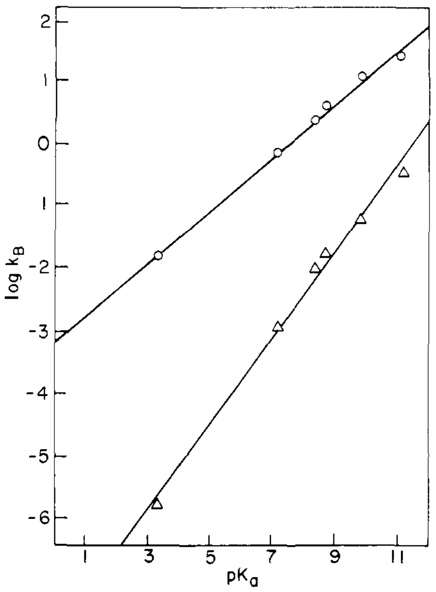


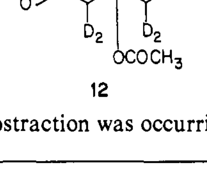
Figure 2. Brønsted plots for the reactions of **7** (open circles) and **1** (open triangles) catalyzed by the tertiary amine catalysts listed in Table I. The least-squares slope of a line through the six points for **7** is 0.42; for **1** it is 0.69. The points for Dabco are corrected as described by Jencks.[7]

contrasts with the β of 0.69 observed for **1**. The β of 0.42 for **7** seems atypical, since $\beta \cong 0.6$ was observed for general base catalysis of proton removal from **2**, **3**, and **4**, as well as from **1**.[1-3]

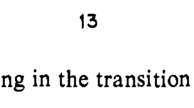
If the values for Dabco·H$^+$ are not included in the Brønsted plots, one obtains $\beta = 0.39$ for **7** and $\beta = 0.61$ for **1**. The latter value is essentially the same as those for proton abstraction from **1**–**4** determined previously[1-3] using a different set of general bases including the weakly basic *N*,*N*-dimethylcyanomethylamine (pK_a = 4.20). Because Dabco·H$^+$ is the only catalyst used in any of these studies which has a positive charge, it is appropriate to ask whether the value of k_B for Dabco·H$^+$ should be included in the determination of β.

Previous studies have indeed demonstrated that positively or negatively charged catalysts often cause deviations from Brønsted plots obtained by using neutral catalysts.[15-17] However, in these cases[15-17] the deviation is in the direction of stabilization of developing charge on the substrate in the transition state by the opposing charge on the catalyst, or of destabilization of developing charge in the transition state by like charge on the catalyst, whereas in the present case the values of k_B for the positively charged Dabco·H$^+$ lie below the lines defined by the k_B's for the other, neutral catalysts despite the fact that negative charge is developing on substrates **7** and **1** in the transition state. It was finally decided that it was more reasonable to include the values for Dabco·H$^+$ in the Brønsted plots shown in Figure 2.

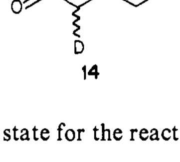
In the cases of **1** and **3**, it was established that proton removal was rate limiting by observation of large, invariant primary kinetic isotope effects for the formation of enone from the α-deuterated substrates **12** and **13**.[1,3] In order to determine whether proton abstraction was occurring in the transition state for the reaction of **7**, analogous experiments were necessary.



12



13

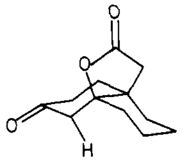


14

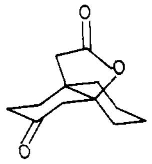
Preparation of deuterated lactone **14** was accomplished by treatment of **7** with a solution of Dabco buffer in D_2O at pH 8.7, followed by acidification with DCl and extraction with ether. Comparison of the rates of hydroxide ion catalyzed conversion of **7** and **14** to **9** yielded a primary kinetic isotope effect, k_H/k_D = 5.0, providing conclusive evidence that carbon–hydrogen bond breaking is involved in the transition state.

Postulation of a Concerted Elimination. The unusual facility of the base-catalyzed elimination reaction of **7** is difficult to explain in terms of a mechanism involving simply rate-limiting proton abstraction to form an enolate anion. The similarity in the rates of the general base catalyzed elimination reactions of **1**–**4**[1-3] suggest that neither slight differences in structure nor large differences in leaving-group ability have much effect on the acidity of the α carbon, ruling against the possibility of an unusually reactive proton in **7**. Since the hydronium ion catalyzed reactions of **1**–**4** are also believed to involve rate-limiting proton transfer, the similarity in the value of $k_H{}^f$ for **7** to the values of k_H for **1**–**4** is further evidence for a normally reactive α proton in **7**.[1-3]

The only plausible suggestion we can make to explain the enhanced reactivity of **7** is that there is strain in the five-membered lactone ring which causes the bond between the ether oxygen and the β carbon to be more easily broken than the corresponding bond in **1**. If this bond in the lactone ring of **7** begins to break as a general base abstracts a proton from the α carbon, a concerted elimination with an enhanced rate could result. Postulation of such an E2 mechanism for the conversion of **7** to **9** requires that there be a trans diaxial arrangement of the proton and the leaving group,[18] which obtains for **7** in conformation **15**, but not in the alternate conformation **16**. On the basis of examination of molecular models and crystallographic results discussed later, a reaction requiring conformation **15** certainly seems reasonable.



15



16

Relief of strain is recognized as a driving force in many chemical reactions,[19,20] and Stirling and co-workers have recently published a number of papers quantitating the effect of leaving-group strain on rates of elimination reactions.[21-26] They have shown that incorporation of a leaving group into a strained ring can cause an acceleration of up to $10^{11.7}$,[21,22] and that in one case, it leads to a change in mechanism from E1cB to E2.[25] Observation of a rate of elimination greater than the rate of deprotonation expected for similar compounds, as is the case for the reactivity of **7** vs. **1**, has also been used in earlier studies as a criterion for assignment of an E2 mechanism.[10,27]

The difference in Brønsted β between **7** and **1**–**4** can also be interpreted as indicative of an E2 mechanism for the elimination reaction of **7**. In the E1cB$_1$ reactions of **1**–**4**, the rate-limiting formation of unstable enolate anion intermediates should, ac-

---

[15] Bell, R. P. "Acid-Base Catalysis"; Clarendon Press: Oxford, 1941; Chapter 5, pp 82–95 and references therein.

[16] Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1973**, *95*, 803–806 and references therein.

[17] Chwang, W. K.; Eliason, R.; Kresge, A. J. *J. Am. Chem. Soc.* **1977**, *99*, 805–808.

[18] Saunders, W. H.; Cockerill, A. F. "Mechanisms of Elimination Reactions"; Wiley: New York, 1973; Chapter 3, pp 105–163.

[19] Greenburg, A.; Leibman, J. F. "Strained Organic Molecules"; Academic Press: New York, 1978; pp 105–112.

[20] March, J. "Advanced Organic Chemistry"; 2nd ed.; McGraw-Hill: New York, 1977; pp 140–146.

[21] Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198–203.

[22] Palmer, R. J.; Stirling, C. J. M. *J. Am. Chem. Soc.* **1980**, *102*, 7888–7892.

[23] Griffiths, G.; Hughes, S.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1982**, 236–237.

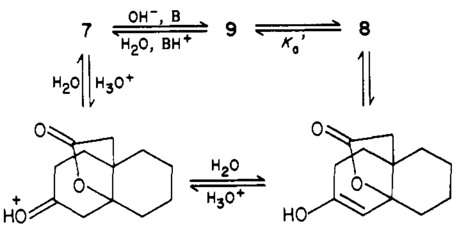
[24] Hughes, S.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1982**, 237–238.

[25] Piras, P. P.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1982**, 658–659.

[26] Piras, P. P.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1982**, 660–661.

[27] Marshall, D. R.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1914–1919.

Scheme II



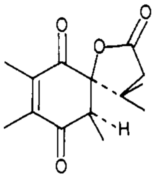
cording to the Hammond postulate,[28] involve a transition state with a large degree of proton transfer and a large value of β (e.g., 0.69 for **1**). The presumed involvement of the leaving group in the case of **7** should result in an earlier transition state with respect to proton transfer, and a smaller value of β, as is observed for **7** (0.42). Bordwell[29] has recently described and discussed the relatively low values of β for E2 elimination reactions, as opposed to proton transfers, in Me_2SO. The other known values of β for E2 reactions are also low (ca. 0.4)[30,31] with the exception of those recently reported by Jencks, in which a change in mechanism from E1cB$_I$ to E2 upon modifying the substrate so it would have a less stable carbanion intermediate while keeping the leaving groups the same was accompanied by an increase in β from ca. 0.7 to ca. 0.9.[32,33]

The proposed mechanisms for the interconversions of **7**, **8**, and **9** are summarized in Scheme II. Hydronium ion catalyzed interconversion of **7** and **8** occurs by a stepwise mechanism involving a transition state in which an added proton is being transferred between water and an enol intermediate. In theory, this reaction should also be subject to general acid catalysis, which should be most effective with the weakest base studied, Dabco·H$^+$. However, as discussed earlier, when Dabco·H$^+$ buffers are used as catalyst, only general base catalysis is observed, and the value of k_B for Dabco·H$^+$ fits reasonably well on the Brønsted plot determined by using stronger bases. This suggests that the Dabco·H$^+$-catalyzed formation of **8** from **7** involves initially the same E2 elimination of **7** to form **9** observed with stronger bases, followed by rapid protonation of **9** to give **8** in the acid medium.

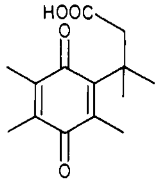
The reaction of **7** is the only example we know of a concerted β-elimination reaction of a compound in which the proton involved is activated by a carbonyl group. For the reaction most closely analogous to that of **7** which has been studied kinetically, Borchardt and Cohen[34] concluded that spirolactone **17** undergoes reversible intramolecular elimination to form enone acid **18** by a stepwise mechanism, on the basis of observation of a change in rate-limiting step with changing buffer concentration. Since a molecular model of **17** indicates that it can readily adopt a conformation which is favorable for a concerted elimination to form **18**, the postulated E2 behavior of **7** must be a consequence of some geometric distortion of its bridged ring system rather than simply the result of the presence of a γ-lactone.

Although E2 eliminations from compounds in which the proton is activated by a carbonyl group are apparently unprecedented, E2 eliminations are often observed when the activating group is CN, SO_2, or Ar.[18,35] As noted earlier, increased stability of intermediate carbanions, as in the case of carbonyl compounds, apparently favors E1cB elimination.[32,33] On the other hand, E2 reactions appear to be favored by better leaving groups. Stirling observed E1cB$_R$ or E1cB$_I$ behavior for substrates $PhSO_2CH_2CH_2Y$ and $NC{-}CH_2CH_2Y$ when Y was OPh, SPh, SO_2Ph, OMes, OTs, OAc, or Cl, but he observed E2 behavior when Y was the better leaving groups Br and I.[35] Similarly, More O'Ferrall observed E1cB reactions for 9-fluorenylmethyl derivatives when the leaving group was relatively poor (OH or OMe)[36,37] and observed E2 reactions when the leaving group was better (Cl or Br).[10] In the case of **7**, of course, the α proton is, as discussed earlier, of comparable acidity to those of **1**–**4**, and the proposed incursion of an E2 mechanism is ascribed to geometric enhancement of leaving-group activity.

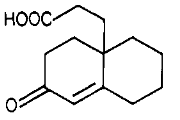
Such a strain-induced concerted mechanism has interesting implications for enzyme-catalyzed β-elimination reactions. The concept of geometric destabilization of a bound substrate has been used by Jencks to help explain enzymatic rate accelerations.[38] In the present context, if an enzyme were to bind a leaving group of a substrate so as to induce strain, this could cause a reaction which would ordinarily involve simply rate-limiting proton abstraction to proceed at an accelerated rate via an E2 mechanism. Assuming that the magnitude of this effect were the same as in the present work, at physiological pH, with a general base of $pK_a = 7$, an increase in the reaction rate of more than 2 orders of magnitude would be observed.



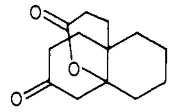
17



18



19



20

Because the proposed E2 mechanism for the reaction **7** → **9** is novel, it was considered important to try to obtain some evidence for the postulated "strain" in lactone **7**. Jones and Kirby[39] have shown that the carbon–oxygen bond lengths in a seris of alkyl aryl acetals are linearly related to the free energy of activation for hydrolysis of these acetals, with lengthening of the C–O bond to be cleaved being associated with increased reactivity. If the enhanced reactivity of **7** relative to **1** is indeed related to partial β C–O bond breaking in the transition state for formation of **9**, then one might expect an analogous lengthening of that bond in **7**, as compared to **1**. In order to test this idea, it was decided to try to determine the X-ray crystal structures of **7** and **1**. A suitable crystal of **7** was easily grown, but, despite persistent efforts, only inadequate crystals of **1** could be obtained. It was then decided to determine instead the structures of **3**, the trans analogue of **1**, and the structures of both cis and trans β-hydroxy ketones **2** and **4**. If the β C–O bond lengths in **2** and **4** were very similar, it might be reasonable to assume that **3** was an adequate model for **1**. Obtaining suitable crystals of **3**, **2**, and **4** proved to be no problem. The details of the crystal and molecular structures of these four compounds will be presented elsewhere,[40] and only the features pertinent to the present discussion will be considered here.

Lactone **7** exists in conformation **15** in the crystal and has a β C–O bond length of 1.486 (5) Å, compared to a value of 1.478 (3) Å for trans-ketoacetate **3**. Allen and Kirby[41] have determined that the average value for the known examples of bonds of this type [$R_3C{-}OC({=}O){-}$] is 1.473 (2) Å. The pertinent bond length for trans-ketol **4** is 1.439 (3) Å, and for cis-ketol **2**, which exists

---

(28) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.

(29) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1983**, *48*, 619–621.

(30) McLennan, D. J. *J. Chem. Soc. B* **1966**, 705–708.

(31) Hudson, R. F.; Klopman, G. *J. Chem. Soc.* **1964**, 5–15.

(32) Alunni, S.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 2052–2060.

(33) Gandler, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 1937–1951.

(34) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9175–9182.

(35) Marshall, D. R.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1898–1909.

(36) More O'Ferrall, R. A.; Slae, S. *J. Chem. Soc., Chem. Commun.* **1969**, 486–487; *J. Chem. Soc. B* **1970**, 260–268.

(37) More O'Ferrall, R. A.; Warren, P. J. *Proc. R. Ir. Acad., Sect. B* **1977**, *77B* 513–521.

(38) Jencks, W. P. *Adv. Enzymol.* **1976**, *93*, 240–249.

(39) Jones, P. G.; Kirby, A. J. *J. Chem. Soc., Chem. Commun.* **1979**, 288–289.

(40) Onan, K. D.; Mayer, B. J.; Spencer, T. A. *Acta Crystallogr., Sect. C* **1984**, *C40*, 1041–1044; 1044–1047.

(41) Allen, F. H.; Kirby, A. J., unpublished results.

in the crystal in a conformation analogous to **15**, the bond length is 1.434 (2) Å. It is difficult to come to any definite conclusion on the basis of these data, but it is fair to say that the β C–O bond in **7** is at least on the border line of being unusually long and could be sufficiently elongated to be consistent with the enhanced reactivity of **7**.[39]

In another attempt to test the idea of strain in the γ-lactone ring of **7**, enone acid **19** was prepared by the method of Becker and Birnbaum,[42] with the hope that **19** could be converted to the presumably unstrained δ-lactone **20**, whose reactivity could then be compared with that of **7**. Unfortunately, all attempts to effect ring closure of **19** to **20** were unsuccessful, perhaps owing to the less favorable entropy for formation of δ- as compared to γ-lactones.[43]

Finally, we decided to study a tricyclic compound similar to **7**, but with a different leaving group, in order to try to gain evidence supporting the proposal that the acyloxyl leaving group of **7** is unusually reactive. In the following paper the synthesis of the ether analogue of **7** and its kinetic behavior in elimination reactions is described.

Experimental Section

Melting points were determined in a Thomas-Hoover apparatus in unsealed capillaries and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 599 spectrophotometer as KBr pellets. NMR spectra (^{13}C and ^{1}H) were recorded in $CDCl_3$ on a JEOL FX-60Q multinuclear Fourier transform spectrometer, with $CDCl_3$ or $CHCl_3$ as the internal standard. Chemical shifts are reported in ppm downfield from Me_4Si. The mass spectra were determined on a Finnegan Model 4000 mass spectrometery by Christopher Hill and Richard Abbott.

Syntheses. Acetoxy ketone **1** was synthesized according to the published procedure[1] and purified by recrystallization from hexane to a constant melting point of 50–51.5 °C. Lactone **7** was also synthesized according to the published procedure,[4] except that equimolar amounts of 2–((carbomethoxy)methyl)cyclohexanone, sodium methoxide, and methyl vinyl ketone were used, and hydrolysis of the reaction mixture with aqueous base was omitted. The yield of **7** was routinely 14–18%.

3,12-Dioxo-11-oxatricyclo[4.4.3.0^{1,6}]tridecane-*2*-*d*$_1$ (14). To a solution of 0.072 g (0.346 mmol) of **7** in 2 mL of CH_3OD (Stohler Isotope Chemicals) and 8 mL of D_2O (Aldrich) was added 0.112 g (1.0 mmol) of Dabco. The mixture was allowed to stand at room temperature for 5 h, neutralized with DCl (20% in D_2O, Diaprep), and extracted with three 10-mL portions of anhydrous ether, and the combined ethereal extracts were dried over $MgSO_4$ and allowed to stand for 48 h. The combined ethereal extracts were evaporated to afford 0.070 g of **14**, mp 128–130 °C. Recrystallization from ether afforded 0.060 g (83%) of **14**: mp 133–134 °C; ^{13}C NMR 48.0 ppm (t); IR 3440 cm^{-1}; mass spectrum, m/e 209 (M^+) (calcd for $C_{12}H_{15}DO_3$, 209).

Amines. The amine catalysts or their hydrochlorides (Aldrich) were purified by two recrystallizations from 1:1 methanol/1-propanol or from ether (Dabco) or by sublimation in vacuo (3-quinuclidinone hydrochloride, 3-quinuclidinol). The pK_a of quinuclidine and the first pK_a of Dabco were determined by half-neutralization at 25 °C with $\mu = 0.4$ (KCl). The pK_a's of the other amines were determined under the same conditions with a Fisher Auto-Burette Model 390 and an Orion Research Model 601A pH meter interfaced to a New England Digital Corporation minicomputer. Data acquisition and analyses of the pK_a's were conducted by using an existing software package written by D. Deuring and D. Saucy of the Dartmouth College Environmental Measurements Laboratory using the method of analysis described by Gran.[44]

Kinetics. The kinetic experiments were performed as previously described,[1] except for the following changes: a Cary 219 spectrophotometer equipped with a wavelength programmer, cell programmer, and coupled, 5-cell, thermostatable sample and reference turrets was used, and five kinetic runs were studied simultaneously. A Corning Model 130 pH meter equipped with a Fisher Microprobe Combination Electrode or a Markson PhlexiMark Pencil Combination Electrode was used. A Pipetman adjustable pipettor with a 1–1000-μL range or a fixed 1000-μL pipettor was used.

Reactions for which the half-life was <5 min were followed by monitoring a single reaction continuously at 247.5 nm. The samples were prepared as previously described.[1] After the addition of 1.0 mL of the solution of **7**, the cuvette was mixed by shaking and was rapidly replaced in the sample turret. For very fast reactions in dilute buffers, the solution of **7** was injected directly into the cuvette in the sample turret. The first 3–5 s of the reactions were missed when these methods were used.

The rate of disappearance of **8** was determined by preparing a solution of **9** in aqueous KOH and adding 1.0 mL of this solution to the appropriate buffer solutions at pH <7. The values of k^f and k^r were determined as described in the text.

In order to obtain equilibrium data, the concentrations of **8** or **9** in solutions of **7** were measured as described in the text. To obtain data at pH ≤3.5, unbuffered HCl solutions were used. From pH 4 to pH 6.5, acetate buffers were used, while at pH ≥7 unbuffered KOH or neutral water was the medium for the equilibrium measurements.

Crystal Data. **2**: $C_{11}H_{18}O_2$, $M_r = 182.3$, monoclinic, $a = 13.643$ (4) Å, $b = 5.989$ (1) Å, $c = 12.265$ (3) Å, $\beta = 93.62$ (2)°, $U = 1000.2$ Å^3, $D_c = 1.210$ g cm^{-3}, $Z = 4$, D_m(flotation) = 1.20 g cm^{-3}, $F(000) = 400$, μ (Cu Kα radiation, $\lambda = 1.5418$ Å) = 6.52 cm^{-1}. Space group $P2_1/a$ by systematic absences: $0k0$ when $k \neq 2n$ and $h0l$ when $h \neq 2n$. **3**: $C_{13}H_{20}O_3$, $M_r = 224.3$, monoclinic, $a = 7.822$ (1) Å, $b = 10.731$ (1) Å, $c = 15.052$ (2) Å, $\beta = 101.02$ (1)°, $U = 1240.1$ Å^3, $D_c = 1.201$ g cm^{-3}, $Z = 4$, D_m(flotation) = 1.19 g cm^{-3}, $F(000) = 488$, μ(Cu Kα radiation) = 6.85 cm^{-1}. Space group $P2_1/n$ by system absences: $0k0$ when $k \neq 2n$ and $h0l$ when $h + l \neq 2n$. **4**: $C_{11}H_{18}O_2$, $M_r = 182.3$, monoclinic, $a = 12.325$ (1) Å, $b = 6.357$ (1) Å, $c = 14.400$ (1) Å, $\beta = 116.70$ (8)°, $U = 1007.9$ Å^3, $D_c = 1.201$ g cm^{-3}, $Z = 4$, D_m(flotation) = 1.19 g cm^{-3}, $F(000) = 400$, μ(Cu Kα radiation) = 6.48 cm^{-1}. Space group $P2_1/c$ (C_{2h}^5) from systematic absences: $0k0$ when $k \neq 2n$ and $h0l$ when $l \neq 2n$. **7**: $C_{12}H_{16}O_3$, $M_r = 208.3$, monoclinic, $a = 7.565$ (2) Å, $b = 10.585$ (3) Å, $c = 7.422$ (2) Å, $\beta = 117.62$ (2)°, $U = 526.6$ Å^3, $D_c = 1.312$ g cm^{-3}, $Z = 2$, D_m(flotation) = 1.30 g cm^{-3}, $F(000) = 224$, μ(Cu Kα radiation) = 7.70 cm^{-1}. Space group $P2_1$ (C_2^2) from systematic absences: $0k0$ when $k \neq 2n$.

Structure Analyses. All unique diffraction maxima $4.0 \leq 2\theta \leq 115.0°$ (**2** and **7**) or $4.0 \leq 2\theta \leq 130.0°$ (**3** and **4**) were collected on a Syntex automated P2$_1$ diffractometer using variable $\theta/2\theta$ scans. The structures were solved by using direct phasing methods and were refined (anisotropic O, N, C; isotropic H) by full-matrix least squares.[45] For **2**, convergence was reached at R 0.037 over 1181 observed [$I > 2.0\ \sigma(I)$] reflections; for **3**, $R = 0.070$ over 1425 reflections; for **4**, $R = 0.066$ over 1197 reflections; and for **7**, $R = 0.039$ over 751 reflections.

Acknowledgment. This research was supported by NSF Grant CHE 7808724 and was presented in part at the Fifth IUPAC Conference on Physical Organic Chemistry at Santa Cruz, CA, Aug 1980. We are grateful to Dr. R. Ditchfield for helpful discussion and to Dr. A. J. Kirby for helpful discussion and disclosure of unpublished results. We also thank Dr. A. J. Kresge and Dr. R. A. Bednar for constructive comments on the manuscript.

Registry No. **1**, 36375-74-3; **2**, 4707-07-7; **3**, 66875-62-5; **4**, 4858-91-7; **7**, 72542-12-2; **8**, 72542-13-3; **9**, 91327-84-3; **14**, 91327-83-2; Dabco, 280-57-9; Dabco·H$^+$, 33937-19-8; D_2, 7782-39-0; quinuclidine, 100-76-5; 3-hydroxyquinuclidine, 1619-34-7; 3-chloroquinuclidine, 42332-45-6; 3-quinuclidinone, 3731-38-2; hydronium ion, 13968-08-6; hydroxide ion, 14280-30-9.

---

[42] Becker, D.; Birnbaum, D. *J. Org. Chem.* **1980**, *45*, 570–578.

[43] Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678–1683. Mandolini, L. *J. Am. Chem. Soc.* **1978**, *100*, 550–554. Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102. Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* **1973**, *95*, 3504–3510. Winstein, S.; Allred, E.; Heck, R.; Glick, R. *Tetrahedron* **1958**, *3*, 1–13.

[44] Gran, G. *Acta Chem. Scand.* **1950**, *4*, 559–577.

[45] All crystallographic calculations were carried out on a VAX 11/780 computer. The principal programs used were FMLS, anisotropic full-matrix least-squares refinement: Ganzel, P. K.; Sparks, R. A.; Trueblood, K. N., UCLA, modified by McPhail, A. T., Duke University; ORTEP, crystallographic illustration programs, Johnson, C. K., Oak Ridge, ORNL-3794; MULTAN 80; for description see: Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. B* **1970**, *B26*, 274–285.